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Precipitated Withdrawal by Pentazocine in Methadone-Maintained Volunteers[1]

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ABSTRACT

Pentazocine is a partial *mu* agonist opioid with one-half to one-sixth the parenteral analgesic potency of morphine. The purpose of this study was to characterize the effects of pentazocine in comparison to naloxone (an opioid antagonist), hydromorphone (an opioid *mu* agonist) and saline in methadone-dependent volunteers by using the same experimental methods used previously in the study of the opioid analgesics buprenorphine, butorphanol and nalbuphine. In a residential laboratory, five volunteer male opioid abusers, maintained on 30 mg p.o. of methadone daily, underwent pharmacological challenges 2 to 3 times per week. Pharmacological challenges consisted of a double-blind i.m. injection of: pentazocine (dose range 7.5–120 mg), hydromorphone (5 and 10 mg), naloxone (0.1 and 0.2 mg) or saline. Injections were given 20 hr after the last dose of methadone. Measures included physiological indices and self-reports and observer ratings of drug effects. Naloxone and hydromorphone produced characteristic antagonist-like and agonist-like effects, respectively, on subjective, observer and physiological indices. Pentazocine produced primarily antagonist-like effects, with higher doses (> = 60 mg) producing significant elevations of visual analog scale ratings of Drug Effects, Bad Effects and Sick; of observer ratings of piloerection, restlessness and adjective scores of opioid withdrawal; as well as increases in blood pressure, heart rate and pupil diameter and decreases in skin temperature. Similar to the previous study of butorphanol, the specific profile of effects produced by pentazocine differed from that produced by naloxone, suggesting non-*mu* effects may modulate the *mu* effects of pentazocine.

Pentazocine is a mixed agonist-antagonist opioid with an analgesic potency estimated to be between one-half and one-sixth that of morphine, depending in part upon the population used in estimating potency (Keats and Telford, 1964; Cass *et al.*, 1964; Beaver *et al.*, 1966; Bellville and Forrest, 1968; Paddock *et al.*, 1969). Pentazocine has a more rapid onset and shorter duration of analgesic activity and respiratory depression compared to morphine (Sadove *et al.*, 1964; Bellville and Green, 1965; Paddock *et al.*, 1969), and analgesia appears to reside in the *l*-isomer (Forrest *et al.*, 1969; Berkowitz, 1974). Whereas Martin (1983) described pentazocine as a *mu* antagonist and *kappa* agonist, evidence from several species suggest pentazocine is better characterized as a *mu* partial agonist with a non-*mu* component of activity.

Studies in several non-human species have demonstrated that pentazocine has both agonist and antagonist activity at the *mu* opioid receptor. By using rats trained to discriminate between saline and an active drug, pentazocine has been shown to be discriminated as morphine-like (Shannon and Holtzman, 1976, 1979) and morphine to be discriminated as pentazocine-like (Kuhn *et al.*, 1976). Discrimination data from the squirrel monkey also suggest pentazocine has a morphine-like component of action (Schaefer and Holtzman, 1981; White and Holtzman, 1982), as do discrimination data from pigeons (Herling *et al.*, 1980; France and Woods, 1985). In the morphine-dependent chronic spinal dog, pentazocine precipitates abstinence (Gilbert and Martin, 1976), although other animal studies have found pentazocine demonstrates either very weak or no antagonism of the effects of morphine (McMillan and Harris, 1972; Downs and Woods, 1976; Shimada *et al.*, 1984).

Evidence for pentazocine's activity at the *mu* receptor in humans is derived from studies in both non- and opioid-dependent subjects, and these studies have also demonstrated both agonist and antagonist effects. Acute single doses of pentazocine in nondependent humans produce morphine-like subjective effects at low doses, although nalorphine-like effects occur at higher doses (Jasinski *et al.*, 1970; Preston *et al.*, 1987; Preston and Bigelow, 1993). Drug discrimination data in humans show that low doses of hydromorphone produce pentazocine-like responding, and pentazocine is identified as hydromorphone-like in a two choice drug discrimination procedure (Bickel *et al.*, 1989; Preston *et al.*, 1989a, 1992). Studies in morphine-dependent humans have shown pentazocine will pre-

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ABBREVIATION: HST, honestly significant difference.

cipitate withdrawal, and pentazocine does not suppress abstinence withdrawal after cessation of chronic morphine dosing (Jasinski *et al.*, 1970).

Discrimination studies using rats (Holtzman and Jewett, 1972) and monkeys (White and Holtzman, 1982) have demonstrated pentazocine also has a non-*mu* effect. In rats trained to discriminate pentazocine from vehicle, stimulus effects of pentazocine can be reversed by high doses of naltrexone (Ukai *et al.*, 1989), suggesting that this non-*mu* activity is an opioid effect. However, this non-*mu* opioid activity does not appear to be *kappa*-mediated in animals. Pentazocine does not generalize to the *kappa* agonist bremazocine in pigeons, but does generalize to the *mu* agonist fentanyl (Picker *et al.*, 1989) and, unlike *kappa* agonists, it does not produce diuresis in rats (Leander, 1983).

In humans, higher doses of pentazocine produce nalorphine-like subjective effects which differ from the effects produced by morphine, further supporting a non-*mu* component to pentazocine's activity (Jasinski *et al.*, 1970; Preston *et al.*, 1987). These nalorphine-like subjective effects were designated as *kappa*-like in Martin's early descriptions of multiple opioid receptors (Martin *et al.*, 1976). In morphine-dependent humans high doses of pentazocine have been found to produce non-*mu*-like effects of psychotomimesis (Jasinski *et al.*, 1970), and occasional reports of hallucinatory effects have also been reported in nondependent clinical populations (Beaver *et al.*, 1968; DeNosaquo, 1969). Low doses of naltrexone block the *mu*-effects of pentazocine and reveal *kappa*-like subjective bad effects and dysphoria, whereas higher doses of naltrexone block both *mu* and non-*mu* effects (Preston and Bigelow, 1993). Thus, although results across species demonstrate pentazocine has a non-*mu* component of activity, between species differences in the characterization of this activity suggest *kappa*-like subjective effects in humans, but a failure to demonstrate *kappa* agonist effects in animals.

Fraser initially described pentazocine as having a lower abuse liability than morphine (Fraser and Rosenberg, 1964) and whereas there were rare case reports of abuse of pentazocine after it became available for clinical use (Keup, 1968; AMA Council on Drugs, 1969; Chambers *et al.*, 1971), it continued to be characterized as having a low abuse potential throughout the mid-1970's (Kelly, 1977). However, in the late 1970's, cases of abuse of the combination of pentazocine and tripelennamine (T's and Blues) began appearing in the Midwest of the United States and in one clinic as many as one-half of heroin users were reporting at least occasional use of the mixture (DeBard and Jagger, 1981; Senay, 1985; Lange and Jasinski, 1986). There was a subsequent decline in pentazocine abuse after the introduction of the combination product pentazocine-naloxone in 1983 (Polkis, 1984).

This study is one in a series characterizing the effects of opioid agonist-antagonists in methadone-dependent volunteers. In previous studies butorphanol produced a naloxone-like withdrawal syndrome, but with some symptoms differing from those produced by naloxone (Preston *et al.*, 1988); nalbuphine produced a withdrawal syndrome indistinguishable from naloxone (Preston *et al.*, 1989b); and buprenorphine produced no significant withdrawal syndrome (Strain *et al.*, 1992). These previous studies have demonstrated that the precipitated withdrawal syndrome can vary as a function of the agonist-antagonist compound.

When compared to earlier studies with morphine-maintained subjects, the present line of investigation with methadone-maintained volunteers also shows the precipitated withdrawal syndrome can vary as a function of the agonist maintenance medication (*e.g.*, Jasinski *et al.*, 1975; Preston *et al.*, 1988). The present study used the methodology of these earlier studies with methadone-maintained volunteers and examined the effects of pentazocine. The purpose was to characterize the profile and time course of the physiological, subjective and behavioral effects of pentazocine in opioid-dependent subjects, by using controls of naloxone and hydromorphone in order to compare pentazocine effects to prototypic withdrawal and agonist effects. In addition, the results from this study can be compared to earlier work on pentazocine precipitated withdrawal in morphine-dependent subjects (Jasinski *et al.*, 1970).

Methods

Subjects. Subjects were six adult male opioid-dependent volunteers. Demographic features are summarized in table 1. All were diagnosed as opioid-dependent by using the Structured Clinical Interview for DSM-III-R, and were otherwise free of major mental illness. Subjects underwent routine medical screening which included history and physical examination, EKG and chemistry, hematology and urinalysis testing. Results were reviewed by a medical staff not involved in the study as investigators, and all subjects were found to be without significant medical problems.

Each participant was enrolled in outpatient methadone treatment and were maintained on 30 mg p.o. daily for a minimum of 2 weeks before beginning the study. During the inpatient portion of the study subjects received doses of methadone at the same time each day, which was 2 hr after the completion of experimental sessions (*i.e.*, 20 hr before the test drug administration). The study was approved by the Institutional Review Board; volunteers gave written informed consent and were paid for their participation.

Study setting. Subjects lived on a 14-bed human behavioral pharmacology residential research unit while participating. Urine samples were collected at admission and at least 3 times weekly, and were tested for the presence of illicit drugs by using an EMIT system (Syva Co., Palo Alto, CA). Breathalyzer testing for alcohol was done on the day of admission and at least twice weekly. No evidence of unauthorized drug or alcohol use during study participation was observed.

Study procedure. This study followed procedures developed by this laboratory for similar studies of butorphanol (Preston *et al.*, 1988), nalbuphine (Preston *et al.*, 1989b) and buprenorphine (Strain *et al.*, 1992). After outpatient stabilization on 30 mg of methadone for a minimum of 2 weeks, participants were admitted and oriented to the unit, consent was obtained and they were introduced to the session room and the staff who would conduct the laboratory sessions. Each subject participated in a minimum of 11 experimental sessions (plus a training session), and typically resided on the unit for 4 weeks. Each session consisted of i.m. injection challenges of one of two doses of the opioid *mu* agonist, hydromorphone, one of two doses of the antagonist, naloxone, one of six doses of the mixed agonist-antagonist, pentazocine or of placebo. After completion of the inpatient portion of the study, subjects returned to the outpatient methadone clinic, where they received a 30-day methadone detoxification, or were assisted in placement in a longer duration drug treatment program.

Laboratory sessions. Sessions were conducted at the same time of day, no more than 3 days per week, separated by at least 48 hr. The session room was located in a suite separate from the residential unit and contained two chairs, an Apple IIe computer and physiological monitoring equipment. Subject and observer measures were presented on the computer screen and responses were entered by using a key pad and joystick.

Sessions lasted 2.5 hr. Fifteen minutes after the start of each session 10 min of base-line physiological data were obtained. All subject and observer questionnaires were completed and two pupil photos were

TABLE 1
Demographics

Participant	Age	Race[a]	Opioid Use	Frequency of Opioid Use	Amount Spent on Opioids	Methadone Dose	Current Prestudy Methadone Treatment
	years		*years*	*times/day*[b]	*$/day*[b]	*mg*	*weeks*
1	34	B	16	2	60	30	8
2	37	B	15	5–6	150–180	30	3
3	33	B	17	3	80	30	3
4	35	B	15	2–3	40–90	30	4
5	38	B	20	3	50	30	2
6	38	B	20	3	50	30	4

[a] B, Black (African-American).
[b] Premethadone treatment.

taken. Thirty minutes after the start of the session the participant received two i.m. injections, one in each arm; blood pressure monitoring was halted during the injections and the injection sites were massaged for 1 min before resuming blood pressure monitoring. The session then continued for 2 hr, with data collected as described below.

Saline was administered in the first session for each subject. This session followed the format of all subsequent sessions, including staff being blind to the drug being administered; however, it served as a training session and was excluded from statistical analyses.

Physiological measures. Physiological measures consisted of heart rate, blood pressure, skin temperature and respiratory rate, and were monitored continuously throughout the session. Heart rate and blood pressure were collected once per minute by using a Sentry II Automatic Blood Pressure Monitor (NBS Medical, Inc., Costa Mesa, CA). Skin temperature was monitored by using a skin surface thermistor (Yellow Springs Instrument Co., Yellow Springs, OH) taped to a finger on the arm without the blood pressure cuff. Respiratory rate was monitored by using a bellows (Lafayette Instruments Co., Lafayette, IN) placed around the lower chest and connected to a pressure-sensitive switch. Data for each measure were collected and stored in 1-min intervals by using an Apple IIe computer (Apple Computer, Inc., Cupertino, CA). Pupil diameter was determined from photographs taken in ambient room lighting using a Polaroid camera with a 2X magnification. Pupil photographs were taken twice 15 min before drug administration and at 15, 30, 45, 60, 90 and 120 min after drug administration. The first predrug pupil photo was used for the baseline measure.

Subject and observer measures. Subjective effect reports and observer rating questionnaires were completed 15 min before and at 15, 30, 45, 60, 90 and 120 min after drug administration. Subjects were instructed to respond describing how they felt at the time the questionnaire was being answered.

Subjects completed visual analog scales, a pharmacological class questionnaire and an adjective rating scale. There were six visual analog scales: High, Drug Effects, Good Effects, Bad Effects, Liking and Sick. Each scale was a horizontal line on the computer screen and the subject positioned an arrow along this line by using a joystick. The ends of the line were labelled "None" and "Extremely," and responses were scored proportionately on a 100-point scale. The pharmacological class questionnaire asked the subject to select 1 of 10 drug classes to which the administered drug was most similar: Placebo, Opioids, Opioid Antagonists, Phenothiazines, Barbiturates and Sleeping Medications, Antidepressants, Hallucinogens, Benzodiazepines, Stimulants and Other. Examples for each drug class were listed. The adjective rating scale (Fraser *et al.*, 1961; Jasinski, 1977) consisted of 37 items which the participant rated on a five-point scale from 0 (not at all) to 4 (extremely). The items in the rating scale were divided into two scales: a 16-item opioid Agonist scale (adjectives associated with morphine-like effects) and a 21-item Withdrawal scale (adjectives associated with opioid withdrawal-like effects). The items in the Agonist scale were: nodding, heavy/sluggish feeling, dry mouth, carefree, good mood, energetic, turning of stomach, skin itchy, relaxed, coasting, soapbox (talkative), pleasant sick, drive, drunken, friendly and nervous. The items in the Withdrawal scale were: muscle cramps, flushing, painful joints, yawning, restless, watery eyes, runny nose, chills or gooseflesh, sick to stomach, sneezing, abdominal cramps, irritable, backache, tense and jittery, sweating, depressed/sad, sleepy, shaky (hands), hot or cold flashes, bothered by noises and skin clammy and damp. The ratings for individual items were summed for a total score for each scale.

Observer ratings included the same adjective rating scale, as well as an assessment for the presence or absence of six signs of opioid withdrawal: lacrimation, rhinorrhea, yawning, perspiration, piloerection and restlessness (Himmelsbach scale, derived from Kolb and Himmelsbach, 1938). Ratings were made by a research technician who was present throughout the session and blind to the drug administered. Observer ratings were done at the same time intervals as were the subject ratings. The adjective rating scale items were similarly summed to produce a total score.

Psychomotor/cognitive performance measures. Two computerized psychomotor/cognitive performance measures were completed by the subject during the session: a recall (memory) task, in which the subject was required to recall eight-digit numbers and a computerized form of the Digit Symbol Substitution Task (McLeod *et al.*, 1982). The tests were completed during the base-line period (15 min before drug administration) and 60, 90 and 120 min after drug administration.

Drugs and doses. Participants ingested a daily p.o. dose of 30 mg of methadone hydrochloride (10 mg/ml) in a cherry flavor liquid concentrate (Mallinckrodt, St. Louis, MO). Eleven drug conditions were tested: placebo, hydromorphone (5 and 10 mg), naloxone (0.1 and 0.2 mg) and pentazocine (7.5, 15, 30, 60, 90 and 120 mg). Commercial preparations of hydromorphone hydrochloride (10 mg/ml; Knoll Pharmaceuticals, Whippany, NJ), naloxone hydrochloride (0.4 mg/1 ml; Abbott Laboratories, North Chicago, IL and DuPont Pharmaceuticals, Wilmington, DE) and pentazocine lactate (equivalent to 30 mg of base/ml; Winthrop Pharmaceutical Division of Sterling Drug, New York, NY) were used.

Hydromorphone, naloxone and pentazocine were diluted to the appropriate volumes with bacteriostatic saline. Normal saline (4 ml) was used for placebo. All doses were given under double-blind conditions in two equal i.m. injections of 2.0 ml each, one to each arm (4 ml total).

The dose schedules for the 11 sessions were derived from a Latin square for 11 subjects; the schedules were modified so that pentazocine doses were always ascending, although the positions of pentazocine administrations within each schedule were not changed. Pentazocine doses were given in ascending order as a safety procedure, because the effect of pentazocine in precipitating withdrawal was not known. The ascending sequence permitted discontinuation if a subject showed an extreme response to a dose of pentazocine. Subjects were assigned one of the 11 schedules by using a random number table.

Data analysis. Five subjects completed all drug and dose conditions; one subject (no. 2, table 1) reported a strong antagonist drug effect during testing with the 90-mg dose of pentazocine and did not receive the 120-mg dose. This subject was excluded from the data analyses reported below, so results for the full dose range of pentazocine could be presented.

The maximum change from base line was determined for each

measure. For most measures this was a peak (increase) effect, although pupil diameter increased for some drug conditions (*e.g.*, naloxone) and decreased for others (*e.g.*, hydromorphone); hence peak and nadir effects were examined for pupil measures. Unless otherwise noted, "peak effect" refers to the value associated with the maximum absolute change from base line.

A conservative one-step procedure, Tukey's HSD, was used to compare peak saline values to the peak value of each active drug condition. The mean square error term needed to perform these tests was calculated by using a repeated measures, two-factor analysis of variance; main effects were the 11 drug conditions and time (base line *vs.* peak effect). Comparisons for which the Tukey q-value was greater than 5.439 ($P < .05$) are reported as statistically significant.

Individual items from the subject-rated adjective scale were compared across conditions by using a repeated measures, one-factor analysis of variance for the mean rating across the five subjects. Tukey's HSD was used for post hoc comparisons.

Results

Table 2 summarizes the results of the post hoc analyses on the subject-rated, observer-rated and physiological measures for peak drug effect compared to peak saline effect. Arrows in table 2 indicate the direction of change and dashes indicate no significant difference was found. The effects of hydromorphone and naloxone were dose-related, as can be seen from table 2. As described more fully below, in general hydromorphone and naloxone produced significant opioid agonist-like and opioid withdrawal-like effects, respectively, whereas the higher doses of pentazocine produced opioid withdrawal effects. The profile of withdrawal effects for pentazocine appeared to differ somewhat from the profile of withdrawal effects produced by naloxone, and there appeared to be a decrease of pentazocine effects with the highest dose (120 mg).

Subjective effects. The low doses of hydromorphone and naloxone produced no significant changes in subjective effects, whereas the higher doses produced changes in several measures (table 2). Hydromorphone (10 mg) produced significantly increased ratings of Drug Effects and on visual analog scale ratings typically associated with opioid agonist effects: High, Good Effects and Liking (fig. 1). Naloxone (0.2 mg) produced significantly increased ratings of Drug Effects and on visual analog scale ratings typically associated with opioid antagonist or withdrawal effects: Bad Effects and Sick (table 2; fig. 1).

The three lowest doses of pentazocine (7.5, 15 and 30 mg) produced no significant changes in ratings of visual analog scale effects, whereas the three higher doses (60, 90 and 120 mg) produced increased peak ratings of Drug Effects and Bad Effects (table 2; fig. 1). The 60-mg dose of pentazocine also produced a significant increase in ratings of Sick (fig. 1), which was approximately half of the rating of the 0.2-mg dose of naloxone (46 *vs.* 83). In addition, pentazocine produced effects on ratings of High which were similar in magnitude to the 10-mg dose of hydromorphone (fig. 1).

Peak adjective Withdrawal scores were significantly elevated for the naloxone (0.2 mg) and pentazocine (60, 90 and 120 mg) conditions (table 2). Figure 2 presents the naloxone and pentazocine results for selected individual items from the adjective rating scale; this figure follows the same format used in earlier papers which examined the effects of butorphanol (Preston *et*

TABLE 2
Summary of peak drug effects

	Naloxone (mg)		Hydromorphone (mg)		Pentazocine (mg)					
	0.1	0.2	5	10	7.5	15	30	60	90	120
Subjective measures										
Visual analog scales										
High	—	—	—	↑*	—	—	—	—	—	—
Drug effects	—	↑**	—	↑*	—	—	—	↑*	↑**	↑**
Good effects	—	—	—	↑*	—	—	—	—	—	—
Bad effects	—	↑**	—	—	—	—	—	↑*	↑*	↑**
Liking	—	—	—	↑*	—	—	—	—	—	—
Sick	—	↑**	—	—	—	—	—	↑*	—	—
Adjective rating scales	—	—	—	—	—	—	—	—	—	—
Agonist	—	—	—	—	—	—	—	—	—	—
Withdrawal	—	↑**	—	—	—	—	—	↑**	↑**	↑**
Observer-rated measures										
Himmelsbach scale										
Total score	↑*	↑**	—	—	—	—	—	—	—	—
Lacrimation	↑**	↑**	—	—	—	—	—	—	—	—
Rhinorrhea		↑**	—	—	—	—	—	—	—	—
Perspiration	—	—	—	—	—	—	—	—	—	—
Piloerection	↑*	↑**	—	—	—	—	—	—	↑**	↑*
Yawning	—	↑*	—	—	—	—	—	—	—	—
Restlessness	—	—	—	—	—	—	—	—	↑*	—
Adjective rating scales										
Agonist	—	—	—	—	—	—	—	—	—	—
Withdrawal	↑**	↑**	—	—	—	—	—	↑**	↑**	↑**
Physiological measures										
Diastolic blood pressure	—	—	—	—	—	—	—	—	—	—
Systolic blood pressure	—	—	—	—	—	—	—	—	↑*	↑*
Heart rate	—	—	—	↑*	—	—	—	—	—	↑**
Respiration	—	—	—	—	—	—	—	—	—	—
Skin temperature	—	↓*	—	—	—	—	—	↓**	↓**	↓**
Pupil diameter	—	↑**	—	—	—	—	↑*	—	↑**	↑**

* $P < .05$; ** $P < .01$.
[a] Arrows show direction of effects relative to placebo. Dashes indicate no significant difference was found.

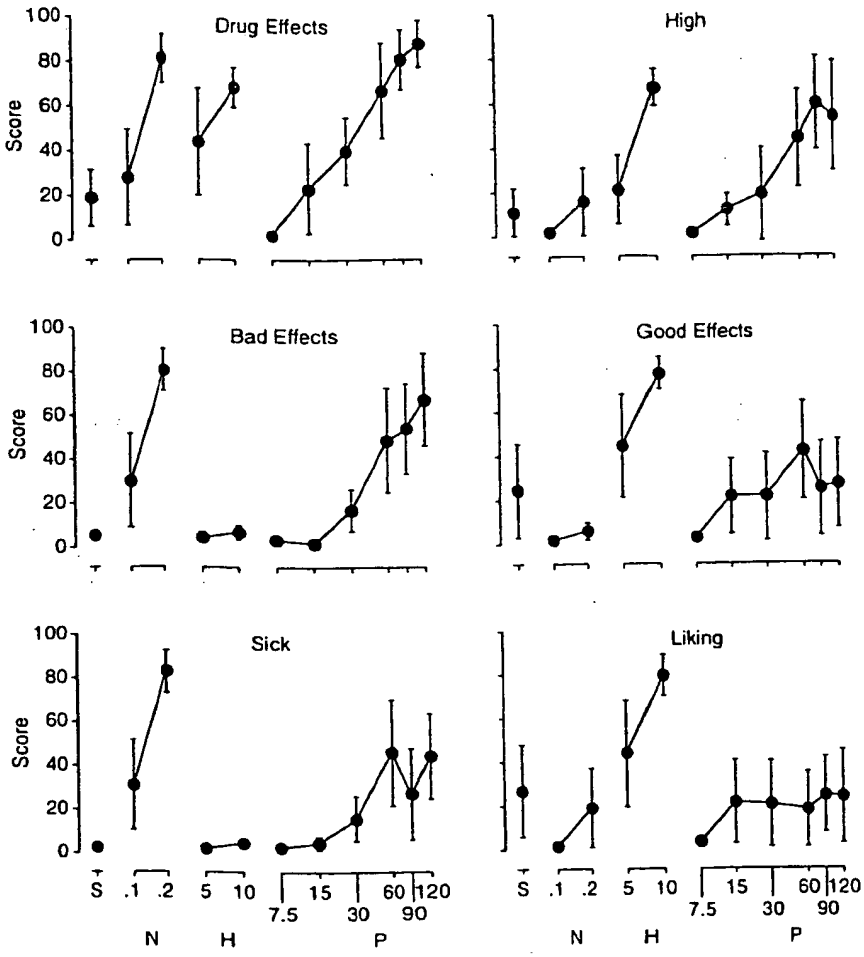

Fig. 1. Effects of saline (S), naloxone (N), hydromorphone (H) and pentazocine (P) on the subject-reported visual analog scale ratings in methadone-dependent volunteers. The maximum possible score was 100. Each point (and bracket) represents the mean peak value (and S.E.) for the five subjects.

al., 1988) and nalbuphine (Preston *et al.*, 1989b), so that comparisons between studies can be made. All these adjectives are opioid-withdrawal items except for heavy/sluggish, turning of stomach and nervous; these three adjectives have been scored as agonist items, but appear to be more sensitive to the effects of naloxone rather than hydromorphone and may need to be reclassified.

The magnitude of ratings for naloxone and pentazocine was comparable across most items (fig. 2). Pentazocine produced a bell-shaped dose-response curve on several adjective items (*e.g.*, sick to stomach, irritable and backache), with highest ratings for the 90-mg dose and some measures showing sharp decreases for the 120-mg dose (*e.g.*, restless). Results of post hoc comparisons for each drug condition *vs.* saline are also presented in figure 2; items marked as significant indicate at least one dose within the drug condition differed from saline. Relative to saline placebo, naloxone produced significantly higher ratings on six items (watery eyes, runny nose, heavy/sluggish, yawning, sleepy and chills/gooseflesh), and pentazocine produced significantly higher ratings on seven items (tense and jittery, chills/gooseflesh, nervous, skin clammy and damp, hot or cold flashes, restless and irritable).

The 13 items from the adjective rating scale not shown in figure 2 are all items on the Agonist scale and are presented in figure 3, which compares pentazocine to hydromorphone. Neither hydromorphone nor pentazocine produced significant changes compared to placebo, although several agonist adjectives showed a U-shaped pattern of responses for pentazocine complementary to the pattern seen with antagonist items. The lowest agonist scores occurred with the 60-mg dose of pentazocine, and this U-shaped effect was most notable on ratings of: carefree, drive, friendly, good mood and relaxed. Unlike the effects of naloxone and pentazocine, hydromorphone did not produce significant differences from saline on any of the adjective items.

Subjects' responses to the drug class identification questionnaire are presented in table 3. Naloxone (0.1 mg) was identified as either placebo (60%) or as an antagonist (40%), whereas the higher dose was identified more frequently as an antagonist (77%). Hydromorphone (5 mg) was identified as either an opioid agonist (47%) or placebo (53%) and 10 mg was identified primarily as an opioid agonist (70%).

The lowest dose of pentazocine (7.5 mg) was always identified as placebo, and the 15-mg dose was characterized as placebo in all but 23% of cases. The first identifications of pentazocine as an antagonist occurred with the 30-mg dose (70% of responses) and the remaining three highest doses were primarily characterized as antagonists (range 60–73%). Other responses for the 60- to 120-mg doses included identifications as an agonist (range, 7–23%), placebo (range, 3–7%), hallucinogen (17%) and stimulant (17%).

Observer-rated effects. Four individual items (lacrimation, rhinorrhea, piloerection and yawning) and the total Himmelsbach score were significantly increased by naloxone (0.2 mg; table 2). Lacrimation, piloerection and the total score were also significantly increased by 0.1 mg of naloxone. None of the doses of hydromorphone were significantly different from saline. Pentazocine produced significant effects for two of the

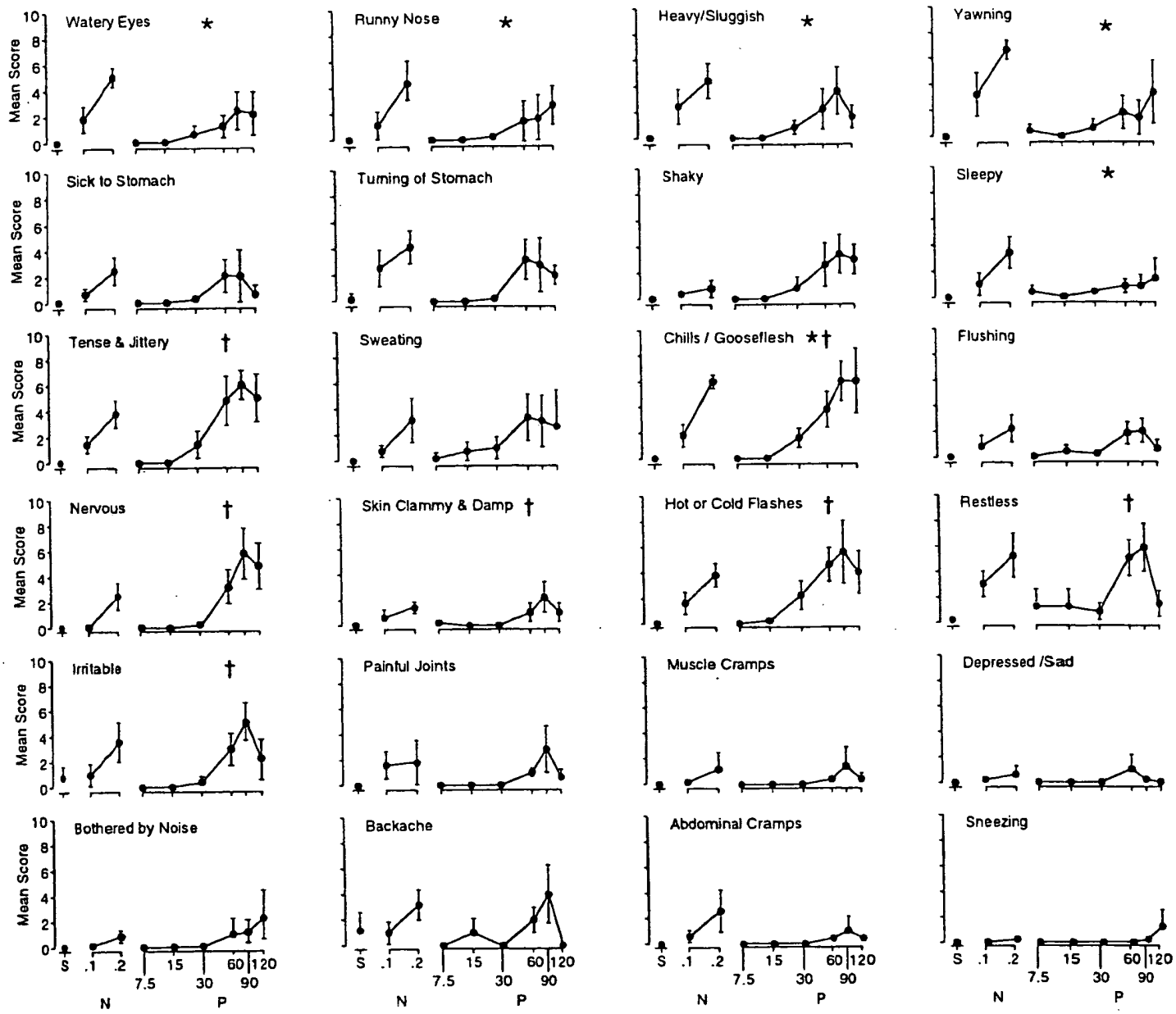

Fig. 2. Effects of saline (S), naloxone (N) and pentazocine (P) on the mean total responses for individual items from the subject-reported adjective rating scale. Each point (and bracket) represents the mean (and S.E.) of the sum of the ratings for the five subjects across six time points; where no brackets are shown, the S.E is smaller than the diameter of the symbol. Turning of stomach, heavy/sluggish and nervous are Agonist Scale items; all others are on the Withdrawal Scale. *Indicates at least one dose within the N condition differed significantly from S; †indicates at least one dose within the P condition differed significantly from S.

observer withdrawal signs, piloerection (90 and 120 mg) and restlessness (90 mg). The dose-response curves for naloxone and pentazocine are presented in figure 4. Naloxone produced dose-related increases in the total score as well as the individual items noted above. Pentazocine's effects were less distinct, with some measures showing increases throughout the dose range (*e.g.*, piloerection and yawning), whereas others showed a bell-shaped dose response (*e.g.*, restlessness and perspiration). The pattern of these observer ratings of withdrawal signs is similar to the pattern of effects on related items in the subject adjective rating scale (fig. 2); dose-related increases occurred on the items gooseflesh and yawning and bell-shaped dose-response curves were found for restless and sweating.

Observer ratings on the adjective rating scale produced significant increases on the Withdrawal scale scores for both doses of naloxone (table 2), as well as the three highest doses of pentazocine. Neither dose of hydromorphone produced significant changes in the observer-rated Agonist adjective scale.

Physiological and psychomotor effects. The results of the physiological monitoring are presented in table 2. Hydromorphone (10 mg) produced a significant increase in heart rate (10 bpm), and naloxone (0.2 mg) produced a significant decrease in skin temperature (7°F). Pentazocine produced increases in systolic blood pressure (15 and 16 mm Hg for the 90- and 120-mg doses, respectively) and heart rate (15 bpm for the 120-mg dose) and significant decreases in skin temperature (9°F for each dose of 60, 90 and 120 mg). Neither naloxone, hydromorphone nor pentazocine had a significant effect on diastolic blood pressure or respiratory rate. Significant pupil diameter increases were seen with naloxone (1.8 mm for the 0.2 mg dose) and pentazocine (1.2, 1.5 and 1.5 mm for the 30-, 90- and 120-mg doses, respectively). None of the drug conditions produced

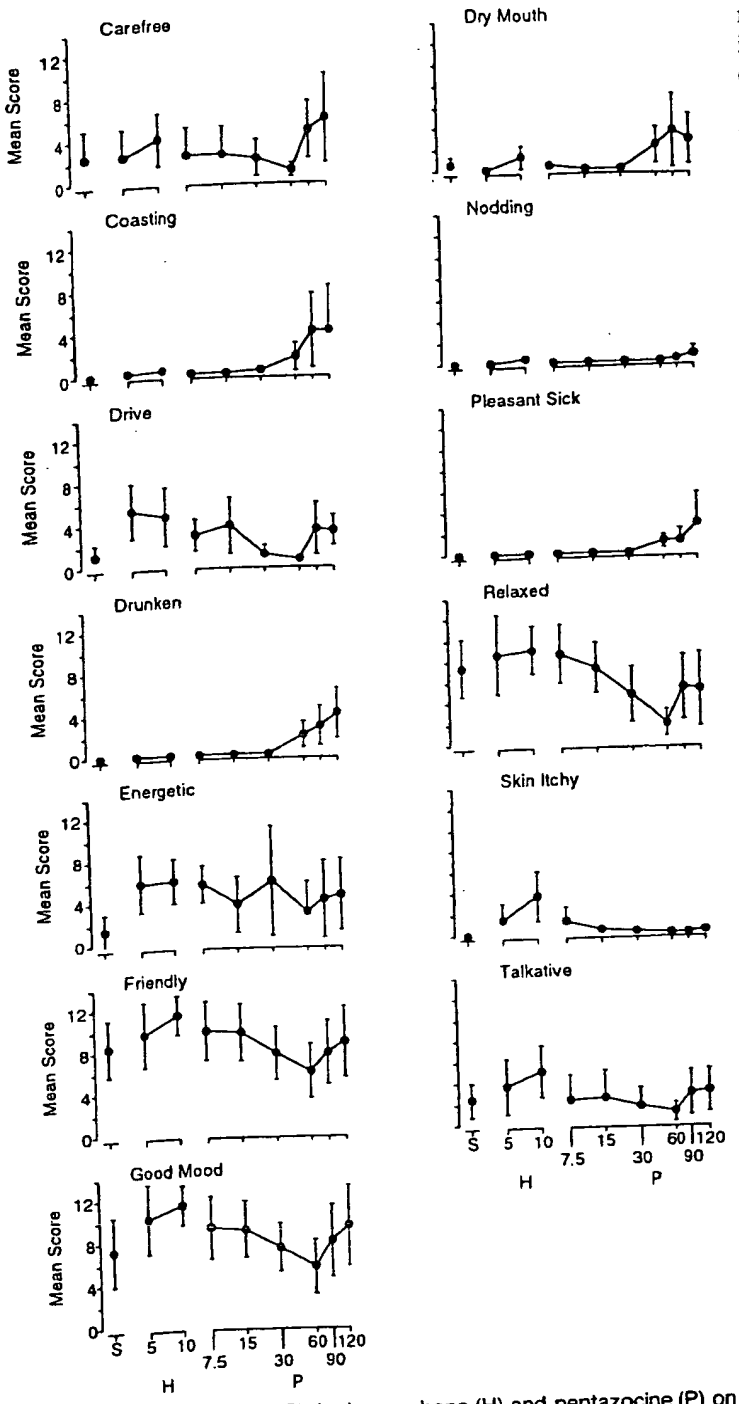

Fig. 3. Effects of saline (S), hydromorphone (H) and pentazocine (P) on the mean total responses for individual items from the subject-reported adjective rating scale. Each point (and bracket) represents the mean (and S.E.) of the sum of the ratings for the five subjects across six time points; where no brackets are shown, the S.E. is smaller than the diameter of the symbol. All items are from the Agonist Scale.

significant effects on the psychomotor/cognitive performance tasks.

Time course of drug effects. Time course effects for three measures are shown in figure 5. Results for all doses of naloxone and hydromorphone and the 30-, 60- and 120-mg doses of pentazocine are presented. The top three panels (fig. 5) show the time course for ratings on the visual analog scale for Drug Effects. Naloxone (0.2 mg) produced a sharp increase in these ratings, with the peak response occurring 15 min after the injection. Hydromorphone (10 mg) produced a smaller and more gradual increase to peak relative to naloxone, with maximum ratings occurring 45 min after the injection. The effects of the 120-mg dose of pentazocine also showed a gradual increase over the first 45 min after the injection, but achieved peak ratings comparable in magnitude to those produced by the 0.2-mg dose of naloxone.

The middle three panels (fig. 5) show responses on pupil diameter. Naloxone (0.2 mg) produced pupillary dilation, with the maximum dilation occurring 15 min after the injection, and continued dilation throughout the session. Hydromorphone produced pupillary constriction of comparable magnitude for the two doses, although the 5-mg dose produced a more gradual constriction over the course of the session. Like naloxone, pentazocine also produced pupillary dilation, although the peak magnitude of dilation was less for pentazocine. Although naloxone had a sharp decrease in pupil diameter between 15 and 30 min after the injection, pentazocine had a more gradual decrease in pupil diameter over the course of the session.

The bottom panels of figure 5 show the response in skin temperature. Naloxone (0.2 mg) produced a gradual decrease and then return to base line in skin temperature, whereas both doses of hydromorphone produced mild sustained increases in skin temperature. The higher doses of pentazocine produced gradual decreases in skin temperature which were comparable in magnitude, but sustained for a longer period than those produced by the higher dose of naloxone.

Discussion

This study found that, in human volunteers maintained on 30 mg p.o. of daily methadone, hydromorphone was identified as agonist-like and naloxone as antagonist-like on subject, observer and physiological measures. Pentazocine's predominant effect was antagonist-like. The relative potencies of pentazocine and naloxone appeared to vary across the signs and symptoms assessed, and pentazocine shared some characteristics with hydromorphone. These results suggest that pentazocine should have a low abuse potential in opioid-dependent individuals.

Pentazocine was similar to naloxone on several measures. It produced antagonist-like effects on visual analog scale ratings of Bad Effects and Sick (table 2; fig. 1), and doses of 30 mg and greater were most frequently identified as an opioid antagonist on the drug identification questionnaire (table 3). In addition, pentazocine produced skin temperature decreases and pupil diameter increases which resembled effects produced by naloxone (table 2). Given previous evidence that pentazocine has *mu* agonist activity (Preston *et al.*, 1987; Preston and Bigelow, 1993), these results are consistent with pentazocine being a *mu* partial agonist.

Whereas pentazocine was antagonist-like, it did differ from naloxone in several ways. The time course of pentazocine's effects tended to show a slower onset and/or dissipation relative to naloxone (fig. 5), suggesting a different pharmacokinetic profile for pentazocine *vs.* naloxone. Higher doses of pentazocine produced visual analog scale ratings of High of comparable magnitude to those produced by hydromorphone (fig. 1), which did not appear to be a nonspecific response to drug detection inasmuch as there were not similar elevations for naloxone. The profile of observer ratings of withdrawal signs also differed for pentazocine *vs.* naloxone (fig. 4), with pentazocine's effects being equal to those produced by naloxone on some measures

TABLE 3

Drug identification responses

Total identifications for each dose condition = 30 (5 subjects × 6 times each). There were no identifications as: Phenothiazines, Barbiturates and Sleeping Medications, Antidepressants and Others.

Drug Administered	Opioid Agonists	Opioid Antagonists	Placebo	Hallucinogens	Benzodiazepines	Stimulants
Placebo	6	2	22	0	0	0
Naloxone						
0.1 mg	0	12	18	0	0	0
0.2 mg	0	23	1	0	0	6
Hydromorphone						
5 mg	14	0	16	0	0	0
10 mg	21	0	9	0	0	0
Pentazocine						
7.5 mg	0	0	30	0	0	0
15 mg	6	0	23	0	1	0
30 mg	1	21	5	0	3	0
60 mg	2	21	2	0	0	5
90 mg	6	18	1	5	0	0
120 mg	7	22	1	0	0	0

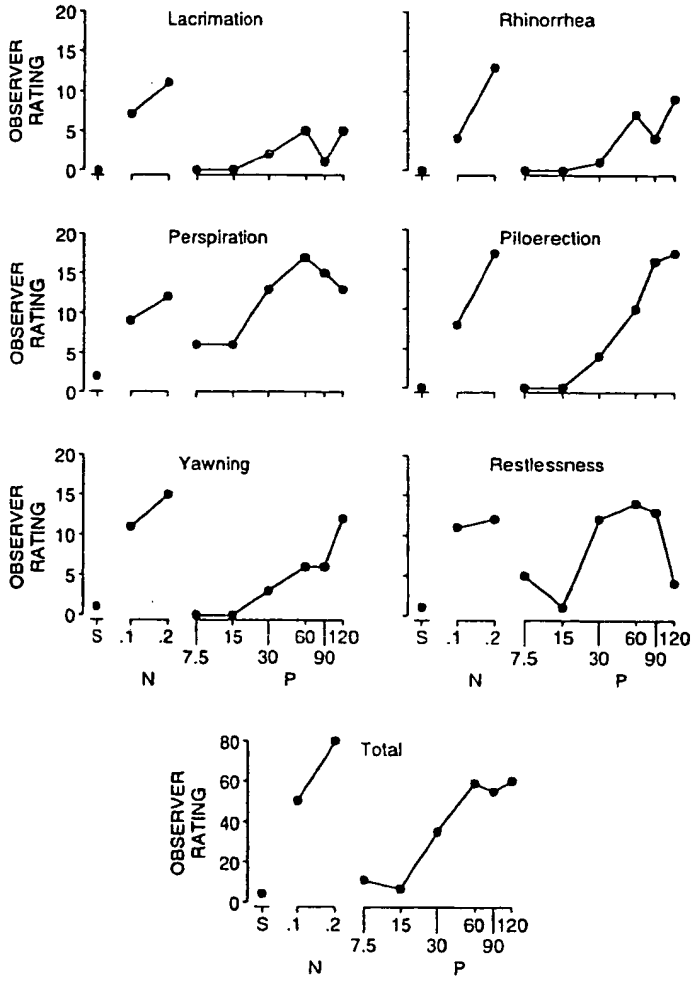

Fig. 4. Effects of saline (S), naloxone (N) and pentazocine (P) on the observer-reported ratings of signs of Withdrawal (the Himmelsbach score) in methadone-dependent volunteers. Each point is the sum of the number of times an observer indicated the presence of the withdrawal sign in each of the five subjects across six time points. Total scores are the sum of all items.

(rhinorrhea, piloerection, yawning and restlessness), but differing from naloxone on others (lacrimation and perspiration).

These differing profiles for naloxone and pentazocine suggest pentazocine has both *mu* and non-*mu* components of activity. Pentazocine's *mu* agonist effects have been well-demonstrated in animals (Shannon and Holtzman, 1976, 1979; Herling *et al.*, 1980; Schaefer and Holtzman, 1981; White and Holtzman, 1982; France and Woods, 1985) and humans (Preston *et al.*, 1987; Preston and Bigelow, 1993), whereas pentazocine's non-*mu* component of activity has been distinguished less clearly. Our laboratory has shown previously that in humans this non-*mu* activity can be blocked by naltrexone, suggesting it is opioid-mediated (Preston and Bigelow, 1993). The results of the present study suggest pentazocine-precipitated withdrawal may be modulated by this non-*mu* opioid activity, accounting for the differing profiles of naloxone and pentazocine.

The sum of ratings for individual adjective items showed pentazocine had a distinctive profile of effects (figs. 2 and 3). Results are presented as the sums of ratings instead of peak ratings in order to facilitate comparison to earlier studies of butorphanol (Preston *et al.*, 1988) and nalbuphine (Preston *et al.*, 1989b). It is useful to compare these results to the ratings produced by butorphanol, which also has been noted to have a profile of effects which was distinguished from naloxone's effects on these ratings (Preston *et al.*, 1988). Across the range of doses tested, naloxone produced higher scores than did butorphanol or pentazocine on a related set of items distinguished by somatic characteristics: watery eyes, runny nose, heavy sluggish and yawning. However, pentazocine produced higher scores than naloxone on four items (shaky, tense and jittery, nervous and hot or cold flashes), whereas butorphanol did not differ from naloxone on these items (Preston *et al.*, 1988). Thus, although pentazocine and butorphanol both differ from naloxone in their specific pharmacologic profile of effects, these results suggest they also differ from each other. Consistent with this observation, in human drug discrimination studies subjects trained to discriminate pentazocine from placebo and hydromorphone identify butorphanol as pentazocine-like (Preston *et al.*, 1989a), whereas subjects trained to discriminate butorphanol from placebo and hydromorphone identify pentazocine in part as both butorphanol- and hydromorphone-like, illustrating that the effects of pentazocine and butorphanol are not identical (Bigelow *et al.*, 1992).

Pentazocine has been noted occasionally to produce psychotomimetic effects (Jasinski *et al.*, 1970; Beaver *et al.*, 1968; DeNosaquo, 1969). Whereas there were five drug identifications of pentazocine as a hallucinogen (table 3), there were a com-

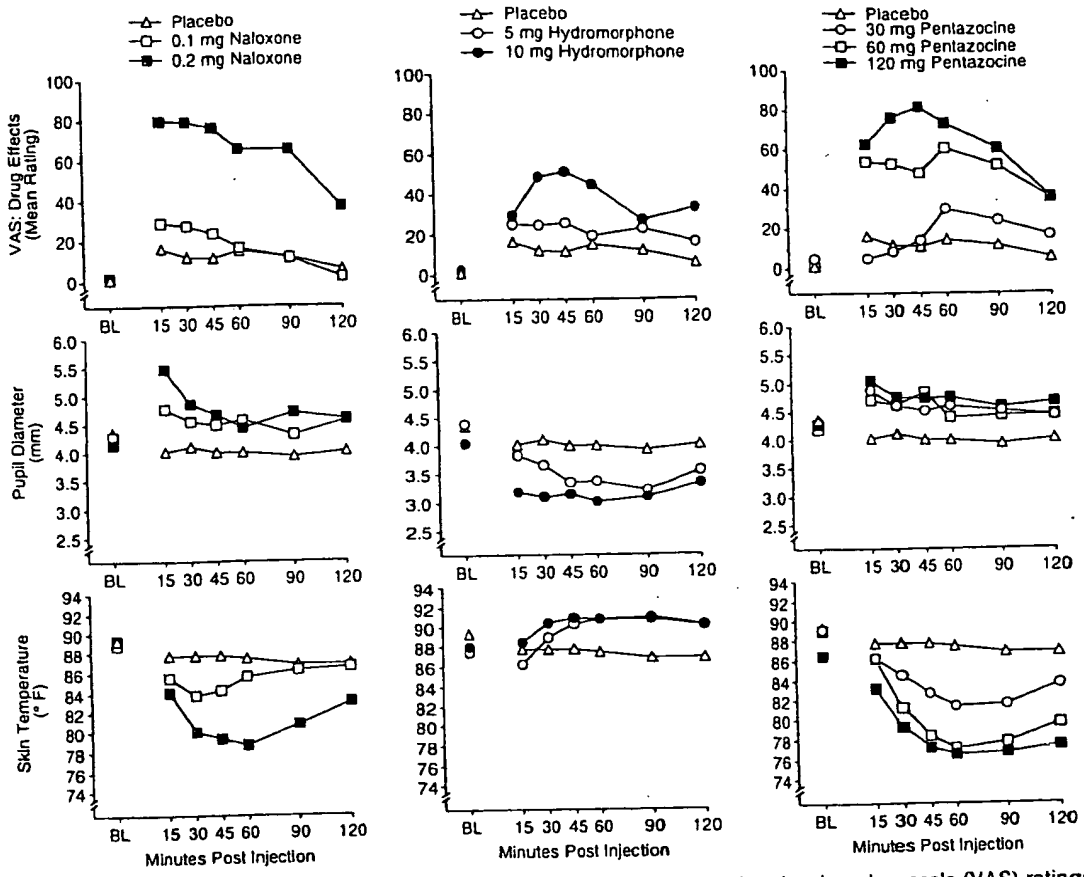

Fig. 5. Time course of the effects of saline, naloxone, hydromorphone and pentazocine on the visual analog scale (VAS) ratings of Drug Effects, and the physiological measures on pupil diameter and skin temperature in methadone-dependent humans. Each point represents the mean value based upon one observation in each of five subjects. For physiological measures, the average over the time interval was calculated for each subject. BL, base line.

parable number of identifications as a benzodiazepine (four) and stimulant (five). Pentazocine was generally well-tolerated, and there were no reports of delusions, hallucinations or other symptoms suggestive of psychotomimesis reported by the participants.

One of the six participants reported strong opioid withdrawal effects with the 90-mg dose of pentazocine, and was not tested with the 120-mg dose. When the results for the 120-mg dose of pentazocine were excluded and analyses utilizing all six subjects were conducted, no differences were found from the pattern of effects reported here. The inclusion of the 120-mg session data revealed a bell-shaped dose-response curve for pentazocine on several antagonist measures (*e.g.*, figs. 2 and 4), and a U-shaped dose-response curve for several agonist measures (fig. 3). Peak/nadir effects for pentazocine occurred in the dose range of 60 to 90 mg, but not all measures showed a reversal of effects at higher doses. If pentazocine has more agonist-like, and fewer antagonist-like effects at higher doses, then there may be some difference in abuse liability with doses greater than those investigated in this study.

A previous study by Jasinski *et al.* (1970) found pentazocine produced a precipitated withdrawal syndrome virtually identical to that produced by nalorphine in subjects maintained on 240 mg of daily morphine, but that unlike the present study doses of 120 to 140 mg of pentazocine also produced psychotomimetic effects which lasted 12 or more hr. This difference in the precipitated withdrawal syndrome produced in morphine *vs.* methadone-maintained subjects has also been noted for butorphanol (Jasinski *et al.*, 1975; Preston *et al.*, 1988), and these differences suggest the dose and type of *mu* agonist maintenance medication used in a precipitated withdrawal study can influence outcomes markedly.

The results of this series of methodologically similar studies of butorphanol, nalbuphine, buprenorphine and now pentazocine provides an opportunity to compare the relative antagonist potencies, analgesic potencies and antagonist/analgesic potency ratios (table 4). Previous studies conducted at our laboratory have shown that butorphanol is a more potent antagonist than nalbuphine, whereas doses of up to 8 mg of buprenorphine have been found to have no antagonist activity in methadone-maintained volunteers (Preston *et al.*, 1988, 1989b; Strain *et al.*, 1992). This study found that pentazocine had a lower antagonist potency than any of these other compounds (60 mg). However, pentazocine also has a low analgesic potency (30 mg) relative to butorphanol (2 mg), nalbuphine (10 mg) and buprenorphine (0.3 mg). Thus, when ranking the relative antag-

TABLE 4
Relative potencies

	Analgesic Dose	Antagonist Dose	Antagonist/Analgesic Ratio
	mg	*mg*	
Buprenorphine	0.3	>8	>26.67
Pentazocine	30	60	2.00
Butorphanol	2	1.5	0.75
Nalbuphine	10	3	0.30

onist/analgesic ratios, pentazocine (2.00) falls between butorphanol (0.75) and buprenorphine (>26.67). As the antagonist/analgesic ratio increases, there should be greater potential for abuse of a compound, and pentazocine's moderately low ratio is consistent with the relative rarity of its abuse before its combination with tripelennamine by the addict community.

The results of this study are consistent with pentazocine's functioning as a partial *mu* agonist, and suggest that it shares pharmacological features with butorphanol. When used alone, pentazocine appears to have a low abuse liability, although it does share some effects with hydromorphone and may be abused when combined with tripelennamine. Methadone-dependent volunteers are able to characterize a specific profile of effects of pentazocine, illustrating the value of this procedure for testing the effects of opioid compounds for clinical abuse liability, as well as showing how the human laboratory can be effectively used to characterize the pharmacological profile of mixed agonist-antagonist opioids.

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